REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow claims 11-18 and 27-41, the only claims pending and currently under examination in this application.

Formal Matters

Claims 11-18 and 27-41 are pending after entry of the amendments set forth herein.

Claims 11-18 and 27-34 were examined. Claims 11-18 and 27-34 were rejected. No claims were allowed.

Claims 1-10 and 19-26 have been cancelled.

Claims 11-18, 27, and 31 have been amended. Support for the amendments can be found in the claims as originally filed and throughout the specification at, for example: original claim 1, and page 6, lines 11-25.

New Claims 35-41 have been added. Support for new the new claims can be found in the claims as originally filed and in the specification at, for example, original claims 13-18.

As the above amendments introduce no new matter to the application, their entry is respectfully requested.

Rejection Under 35 U.S.C. § 101

Claim 11-17, 27-29 and 31-33 have been rejected under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. As suggested in the Office Action, the claims have been amended to recite "non-human". In view of the amendment to the claims, this rejection may be withdrawn.

Rejection Under Statutory-Type Double Patenting

Claims 11-18 and 27-34 have been provisionally rejected under the statutory-type double patenting for allegedly being the same invention as that of claims 11-18 and 27-34 of co-pending Application No. 10/803,550. This rejection is respectfully traversed.

A Terminal Disclaimer is filed herewith in view of claims 11-18 and 27-34 of co-pending Application No. 10/803,550. Applicant notes that the filing of a terminal disclaimer is not an admission of the propriety of a rejection which has or may be applied based on double patenting.[1] However, and solely to expedite prosecution, a Terminal Disclaimer is filed to obviate such a rejection.

Therefore, Applicants respectfully request that this rejection be withdrawn.

Rejection Under Obvious-Type Double Patenting

Claims 1-17, 25, 31, and 36 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 8-17 of U.S. Patent No. 6,475,798. This rejection is respectfully traversed.

The claims of the present application are directed to methods of inserting an exogenous nucleic acid into the genome of a non-human and non-Drosophilidae animal, using a P-element derived vector that comprises a pair of P-element transposase recognized insertion sequences flanking a **single** transcriptionally active gene that comprises the exogenous nucleic acid.

In contrast, U.S. Patent No. 6,475,798 is directed to methods of inserting an exogenous nucleic acid into a non-insect target cell using a vector comprising a pair of P-element transposase sequences flanking at least **two** transcriptionally active genes.

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1 Quad Environmental Technologies Corp. v. Union Sanitary District, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991). The court indicated that the "filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection."

As set out in MPEP § 804 (see section II. B. 1.), in determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is - does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the cited patent or application? An "obviousness-type" nonstatutory double patenting rejection might be appropriate only when the answer is "yes". A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. § 103" except that the patent principally underlying the double patenting rejection is not considered prior art.[2] Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a § 103 obviousness determination.[3]

Moreover, MPEP § 2144.08 (II) states the following:

> The patentability of a claim to a specific compound or subgenus embraced by a prior art genus should be analyzed no differently than any other claim for purposes of 35 U.S.C. 103.
>
> ...
>
> **The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness**. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) (emphasis added)

As such, while the scope of the claims of the cited reference are directed to a broad genus of methods that may encompass methods using a vector that includes a **single** transcriptionally active gene, claims directed to the narrower species are patentable within the broader genus. Therefore, the Applicants respectfully request that this rejection be withdrawn.

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2 *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967).

3 *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). As summarized at MPEP § 804, the factual inquiries are as follows:

(A) Determine the scope and content of a patent claim and the prior art relative to a claim in the application at issue;
(B) Determine the differences between the scope and content of the patent claim and the prior art as determined in (A) and the claim in the application at issue;
(C) Determine the level of ordinary skill in the pertinent art; and
(D) Evaluate any objective indicia of nonobviousness.

Rejection Under 35 U.S.C. § 112, First Paragraph – Enablement

Claims 11-18 and 27-34 have been rejected under 35 U.S.C. § 112, first paragraph on the basis that the specification allegedly does not enable any person skilled in the art to which it pertains, or which it is most closely connected, to make and use the claimed invention commensurate in scope with the claims. The Office Action does acknowledge that enablement is present for making a transgenic mouse using a P-element derived vector comprising a pair of P-element transposase recognized insertion sequences flanking a transcriptionally active gene, wherein the transposase domain is provided on the same vector or a second vector. The Applicant respectfully traverses this rejection as it is applied to the pending claims.

As the Applicants understand it, the Office Action asserts that the specification does not provide enablement for making any transgenic animal commensurate with the scope of the claims.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation."[4]

Disclosure of the Present Application

The Applicants maintain that the present application provides sufficient disclosure to enable the invention to the full scope of the pending claims. The present specification clearly details the preparation and production of such transgenic animals. Beginning on page 10, the specification provides a detailed disclosure of how to generate such animals using the P-element derived vector and a variety of well known nucleic acid delivery techniques, as well as references describing such techniques in greater detail. Moreover, the specification further provides working examples showing use of such vectors in generating transgenic rodents. Accordingly, the Applicants

4. *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

maintain that the specification fully demonstrates that such non-human and non-drosophilidae transgenic animals according to the pending claims without practicing undue experimentation.

Furthermore, at the time the present application was filed, methods of generating transgenic non-human and non-drosophilidae animals were well known. For example, methods of generating transgenic frog embryos were known (see Exhibit A: Amaya et al., *Methods Mol. Biol.*, 1999, 97:393-414) and methods of generating transgenic zebrafish were known (see Exhibit B: Gaiano et al., *Proc. Nat'l Acad, Sci. USA*, 1996, 93(15):7777-7782), both of which are non-human and non-drosophilidae transgenic animals.

In addition to standard methods of generating transgenic animals, such as DNA microinjection, at the time the present application was filed methods of overcoming hurdles faced in generating transgenic animals using standard techniques were also well known. For instance methods of using inducible gene expression systems, such as the tetracycline regulateable system for controlling gene function in transgenic animals (see Exhibit C - Saez et al., *Curr. Opin. Biotech.*, 1997, 8(5):608-616), and other methods of improving strategies for generating transgenic animals (see Exhibit D: Jacenko et al., *Methods Mol. Biol.*, 1997, 62:399-424; Exhibit E: Cameron et al., *Mol. Biotech.,* 1997, 7(3):253-265) were well documented.

Accordingly, the Applicants maintain that once transgenesis is demonstrated in one species, as detailed in the present specification and described above, it is reasonable to conclude that the methods could be extrapolated to other animals in a similar manner without undue experimentation. Therefore, once the Applicants demonstrated the possibility of the described method with one species, it is reasonable to conclude that such methods can be used to generate transgenic animals of different species using a vector that comprises a pair of P-element transposase recognized insertion sequences flanking an exogenous nucleic acid with a reasonable amount of experimentation.

Therefore, the Applicants assert that the methods disclosed in the present specification in conjunction with the knowledge available in the art at the time the present application was filed, would enable one of ordinary skill in the art to practice the invention to the full scope of the claims.

In re Wands Factors

In addition to the above, application of the *In re Wands* test to the facts of the present application leads to the conclusion that the presently pending claims are fully enabled, as demonstrated below.

Under *In re Wands*, a determination of enablement requires consideration of eight factors, including: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[5] Accordingly, under *In re Wands*, a determination of enablement is based on the combination of the factors, taken as a whole, not based solely on a single factor.

In the present application, the Applicant further maintains that the specification, coupled with the information known in the art, would enable one skilled in the art to use the invention without undue experimentation. However, in order to provide structure to the Applicant's response, each of the relevant enablement factors is further discussed in detail below.

(a) the unpredictability in the art and the quantity of experimentation necessary

The Applicant notes that the courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP § 2164.01.[6] Accordingly,

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5. *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

6. See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

the Applicant's citation of *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, in the previous response was to emphasize that where the "experiments are empirical in nature," as in the case of the present application, the court found that no undue experimentation is required.[7]

In citing the research publications the Applicant have sought to establish that the field of generating transgenic non-mammalian animals is not as unpredictable as stated by Examiner. The publications cited above represent only a small fraction of the total number of publications demonstrating the successful generation of transgenic non-mammalian animals. Furthermore, the cited research publications establish that in order to make and use the transgenic animal models according to the full scope of the claims in the present application, undue and excessive experimentation would not be required.

The methods disclosed in the cited references used to generate the transgenic non-human and non-drosophilidae animals were not exactly the same as the method disclosed in the present application. However, the publications have been cited to establish that by reporting the successful generation of non-human and non-drosophilidae transgenic animal models, the cited publications have substantiated the Applicant's position that the field is not as unpredictable as asserted by the Examiner.

Therefore, since the field is not unpredictable, the fact that the experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation, especially if the experimentation in empirical in nature. Accordingly, the Applicant maintains that the "how to make" and "how to use" requirements of 35 U.S.C. §112, first paragraph, have been fulfilled.

As such, the Applicant maintains that the art is replete with successful attempts at generating non-human and non-drosophilidae transgenic animals. Therefore, the field cannot be as unpredictable and requiring of undue and excessive experimentation as the Examiner stresses. As such, the Applicant respectfully submits that the specification coupled with the information available in the art, at the time the application

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7 *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986).

was filed, would enable one skilled in the art to use the invention without undue experimentation.

(b) the breadth of the claims and the amount of direction or guidance presented

The Applicants argue that the requirement for guidance in the specification shall be taken in conjunction with the guidance available in the art. As noted above, other methods of generating non-human and non-drosophilidae transgenic animals are disclosed in the art. One skilled in the art of methods involving manipulating DNA and performing cell-based assays would be able to combine the guidance in the disclosure and the guidance available in the art to practice the claimed invention.

Accordingly, the Applicant maintains that the guidance provided in the specification and highlighted in the previous response, when taken in conjunction with the other enablement factors under *In re Wands*, provides the requisite amount of direction and guidance for a person skilled in the art to make and practice the invention to the full scope of the pending claims.

(c) the presence or absence of working examples

The Applicant respectfully notes that under the *In re Wands* factors for determining compliance with the embalmment requirement under Title 35 U.S.C. §112, first paragraph, the presence or absence or working examples is but a single factor to be taken in consideration with the other factors. As such, under *In re Wands*, the presence or absence of working examples is weighed against the other factors, such as the availability in the art of general guidelines relevant to the claimed invention and guidance provided in the specification.

Moreover, the Applicants cite *In re Robbins* and *In re Borkowski* to emphasize that compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed.[8] Accordingly, the specification need not contain a working example if the invention is

8 *In re Robins* 166 U.S.P.Q. 552 (CCPA 1970); *In re Borkowski,* 164 U.S.P.Q. 642 (CCPA 1970).

otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[9]

However, as the Examiner notes in the Office Action, the present application does contain working examples demonstrating the creation of transgenic mice using the P-element derived vectors. Therefore, the working examples, taken in conjunction with the general guidelines regarding creation of transgenic non-human and non-drosophilidae animals available in the art and the guidelines disclosed in the specification, provides one skilled in the art adequate enablement to practice the claimed invention.

Accordingly, the Applicant maintains that the present application does enable a person skilled in the art, through the specification as well as the working example, sufficient enablement to apply the teachings in the specification in conjunction with the relevant art to make and use the claimed invention.

(d) the relative skill of those in the art

The Applicants maintain that the present invention involves methods of manipulating DNA and performing cell-based assays. As such, the Applicant notes that the skill level of an artisan, such as a laboratory technician or scientist with experience in molecular biology or the equivalent of a doctoral degree in molecular biology techniques, in using such methods is high.

In sum, the Applicant maintains that the enablement requirement has been met because a) the amount of experimentation required to create a non-human and non-drosophilidae transgenic animal would not be undue and excessive b) working examples have been provided, c) guidance is given on how to generate and use such animal models, and d) one of skill in the art would be able to perform the experiments as a matter of routine. The specification, therefore, provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

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9. *In re Borkowski*, 164 USPQ at 642.

As such, for at least the reasons described above, claims 11-18 and 27-34 are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection of claims 11-18 and 27-34 under 35 U.S.C. §112, first paragraph be withdrawn.

Rejection Under 35 U.S.C. § 102

Claims 11-18 and 27-34 have been rejected under 35 U.S.C. § 102(e) for allegedly being anticipated by Fogarty et al. (U.S. Patent No. 6,475,798). In view of the amendments to the claims, this rejection may be withdrawn.

As noted above, the claims of the present application are directed to methods of inserting an exogenous nucleic acid into the genome of a non-human and non-Drosophilidae animal, using a P-element derived vector that comprises a pair of P-element transposase recognized insertion sequences flanking a **single** transcriptionally active gene that comprises the exogenous nucleic acid.

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987). See also, Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001 (Fed. Cir. 1991).

Since Fogarty et al. fails to teach a vector comprising a **single** transcriptionally active gene flanked by a P-element transposase recognized sequences, the cited reference fails to disclose each and every element found in the claims of the present invention. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102 or § 103

Claims 11-18 and 27-34 have been rejected under 35 U.S.C. § 102(b) for allegedly being anticipated, or in the alternative, under 35 U.S.C. § 103(a), for allegedly

being rendered obvious by Khillan et al., Dev. Bio. 1985 109:247-250 (*hereinafter* "Khillan et al."). In view of the amendments to the claims, this rejection may be withdrawn.

The cited reference Khillan et al., discloses transgenic mice comprising a **single** full-length P factor from Drosophila melanogaster (see Figure 4, page 249).

In the spirit of expediting prosecution and without conceding as to the correctness of the rejection, the claims have been amended to recite "**pair of P-element transposase recognized insertion sequences flanking said exogenous nucleic acid**".

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987). See also, Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001 (Fed. Cir. 1991).

Since Khillan et al. fails to teach a transgenic animal comprising a **pair** of P-element transposase recognized sequences, the cited reference fails to disclose each and every element found in the claims of the present invention. As such, Claims 11-18 and 27-34 are not anticipated under 35 U.S.C. § 102(a) by the cited reference. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Conclusion

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number TOSK-007CON

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 2-27-2006

By: _____
Edward J. Baba
Registration No. 52,581

Date: 2.27.06

By: _____
Bret E. Field
Registration No. 37,620

Enclosure:

- Exhibit A: Amaya et al., *Methods Mol. Biol.*, 1999, 97:393-414.
- Exhibit B: Gaiano et al., *Proc. Nat'l Acad, Sci. USA*, 1996, 93(15):7777-7782.
- Exhibit C: Saez et al., *Curr. Opin. Biotech.*, 1997, 8(5):608-616.
- Exhibit D: Jacenko et al., *Methods Mol. Biol.*, 1997, 62:399-424.
- Exhibit E: Cameron et al., *Mol. Biotech.*, 1997, 7(3):253-265.
- Terminal Disclaimer in view of co-pending Application No. 10/803,550.

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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